

Obinutuzumab and ibrutinib induction therapy followed by a minimal residual disease-driven strategy in patients with chronic lymphocytic leukaemia (ICLL07 FILO): a single-arm, multicentre, phase 2 trial

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Obinutuzumab and ibrutinib treatment induction followed by a minimal residual disease-driven strategy in chronic lymphocytic leukaemia (ICLL-07 FILO): a single arm, multicentre, phase 2 trial

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Link to study protocol:
https://clinicaltrials.gov/ct2/show/NCT02666898

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Supplementary appendix, current 3 tables, 1 figure, list of participating sites, protocol synopsis

Previous data presentations for part 1 (chemotherapy-free induction):

- Oral presentation at 59th Annual Meeting of the American Society of Hematology, Atlanta, GA, USA, 9−12 December 2017. Michallet A-S, Dilhuydy MS, Subtil F, et al. Phase II, multicenter trial, exploring "chemo-sparing" strategy associating obinutuzumab+ibrutinib followed by a MRD driven strategy, in previously untreated symptomatic medically fit chronic lymphocytic leukemia patients (CLL): preliminary results of the induction phase of the ICLL-07 FILO study. *Blood* 2017; **130 (Suppl 1)**: 497 (abstract).

- Oral presentation at 23rd Congress of the European Hematology Association, Stockholm, Sweden, 14−17 June 2018. Michallet A-S, Dilhuydy MS, Subtil F, et al. S804 High rate of complete response but minimal residual disease still detectable after first-line treatment combining obinutuzumab and ibrutinib in chronic lymphocytic leukemia. *Hemasphere* 2018; **2 (Suppl 1)**: 350 (abstract).

Previous data presentation for primary results (chemotherapy-free induction followed by MRD-driven strategy):

- Poster presentation at 60th Annual Meeting of the American Society of Hematology, Atlanta, GA, USA, 1−4 December 2018. Michallet A-S, Dilhuydy MS, Subtil F, et al. High percentage of complete response (CR) with undetectable bone marrow minimal residual disease (MRD) after chemo-sparing and MRD-driven strategy for untreated fit CLL patients: Final results of the ICLL-07 FILO trial. *Blood* 2018; **132 (Suppl 1)**: 1858 (abstract).

Summary

Background In chronic lymphocytic leukemia (CLL), achievement of complete response (CR) with bone marrow minimal residual disease (MRD) <0·01% (<1 CLL cell/10,000 leukocytes) has demonstrated associations with longer progression-free survival. Our ongoing multicentre, phase II trial aimed to explore the rate of CR with bone marrow MRD <0·01% after obinutuzumab and ibrutinib induction for nine months then an MRD-driven strategy for six additional months.

Methods In ICLL-07 (NCT02666898), previously untreated, medically fit adults with CLL and no 17p deletion initially received eight obinutuzumab 1000 mg iv doses over 6x4-weekly cycles and ibrutinib 420 mg po daily for nine months. Following assessment at Day 1, Month 9, patients in CR with bone marrow MRD <0·01% continued only ibrutinib 420 mg po daily for six additional months. Otherwise, patients received 4x4-weekly cycles of fludarabine/cyclophosphamide and obinutuzumab 1000 mg iv, alongside continuing ibrutinib. Primary objective was to demonstrate a 30% or higher rate of CR (iwCLL 2008 criteria) with bone marrow MRD <0·01% (by 8-colour flow cytometry) at Day 1, Month 16.

Findings Between 27/10/2015 and 16/05/2017, 135 patients were enrolled. At Month 9, following obinutuzumab and ibrutinib induction, 7·7% of evaluable patients (10/130) reached CR with bone marrow MRD <0·01%; thus, most patients received 4x4-weekly cycles of FC and obinutuzumab, alongside ibrutinib. At Month 16, rate of CR with bone marrow MRD <0·01% was 62% in intent-to-treat (ITT, 84/135, 90% confidence interval [CI]: 55%−69%; primary endpoint) and 74% in evaluable patients (84/113, 90% CI: 67%−81%). Forty-nine serious adverse events occurred, most frequently infections, and three deaths were reported (accidental fall, Month 7; unexplained sudden death, Month 8; Hodgkin lymphoma Epstein-Barr virus-associated haemophagocytosis, Month 23, i.e. 7 months after last FC and obinutuzumab cycle).

Interpretation Obinutuzumab and ibrutinib induction followed by an MRD-driven strategy yielded a 62% ITT rate of CR with bone marrow MRD <0·01% at Month 16. This efficacy rate far exceeds the primary objective, and to our knowledge is higher than that reported to date for any first-line regimen based on chemotherapy plus either rituximab or only obinutuzumab; however, randomised evidence will be needed to conclude superiority.

Funding ROCHE, JANSSEN

Research in context

Evidence before this study

We searched PubMed with the terms "chronic lymphocytic leuk* AND minimal residual disease" (Clinical Trial filter; no language or date limits) and identified bone marrow minimal residual disease (MRD) findings from trials that enrolled previously untreated, medically fit patients with chronic lymphocytic leukaemia (CLL). We also used relevant publications from our own files. Prior to the ICLL-07 trial start in November 2015, six cycles of fludarabine, cyclophosphamide and rituximab (FCR) had reported rates of complete response (CR) with bone marrow MRD <0·01% that were typically under 30%. Bone marrow MRD <0·01% had demonstrated associations with longer progression-free and overall survival after first-line FCR. No study had reported MRD data with first-line obinutuzumab- or ibrutinib-containing regimens in CLL.

Added value of this study

ICLL-07 was the first trial to explore chemotherapy-free induction with obinutuzumab and ibrutinib followed by an MRD-driven strategy in which immunochemotherapy was given only in cases of partial response (PR) or detectable bone marrow MRD. This experimental strategy achieved a 62% intent-to-treat (ITT, 84/135 patients enrolled) rate of CR with bone marrow MRD <0·01% in previously untreated, medically fit patients with CLL and no 17p deletion. This was more than double that typically reported for six cycles of FCR (under 30%) in a similar population, and the primary objective was thus exceeded by far. Of note, our trial data were exhaustive, with 84% (113/135) of patients evaluable for both clinical response and bone marrow MRD at Month 16.

Implications of all the available evidence

In previously untreated, medically fit patients with CLL, there is current research interest in potentially sparing some patients with a good prognosis from the adverse effects of the standard six cycles of fludarabine, cyclophosphamide and rituximab (FCR), as well as improving survival outcomes. Evidence from patients treated with immunochemotherapy suggests that bone marrow MRD <0·01%, in addition to being a deep measure of treatment

response, represents a surrogate marker for progression-free survival. The 62% ITT rate of CR with peripheral blood and bone marrow MRD <0·01% achieved with our experimental strategy is superior to that reported for any first-line regimen based on chemotherapy plus either rituximab or only obinutuzumab. Promising findings are emerging from other trials evaluating first-line strategies incorporating non-chemotherapeutic agents in medically fit patients with CLL. Longer-term outcomes from ICLL-07 and these other trials are awaited.

Introduction

Fludarabine, cyclophosphamide and rituximab (FCR) immunochemotherapy, given for six cycles, is considered as the gold standard for first-line treatment of medically fit patients with chronic lymphocytic leukaemia (CLL) and no 17p deletion.[1,2] With FCR, reported complete response (CR) rate in the first-line CLL setting is 33–68%.[1,3-7] However, irrespective of the clinical response status, CLL cells can often remain in the peripheral blood and/or bone marrow, and reported rate of CR with bone marrow MRD <0·01% with FCR is typically under 30%.[3-6,8] Presence of residual CLL cells has demonstrated associations with poorer progression-free survival (PFS)[4,5,7,9] and overall survival (OS).[4,5,7] This suggests that detection of minimal residual disease (MRD) has powerful value as a prognostic factor and as a PFS surrogate primary endpoint in clinical trials. For this reason, guidelines from the International Workshop on CLL (iwCLL) recommend assessment for MRD in clinical trials, with undetectable MRD defined as <0·01% (<1 CLL cell per 10,000 leukocytes, 10^{-4}) in the peripheral blood or bone marrow.[10,11]

In previously untreated, medically fit patients with CLL, there is current research interest in improving survival outcomes and potentially sparing chemotherapy in some patients with good prognosis. Several non-chemotherapeutic agents demonstrating initial activity in CLL have recently been developed, notably agents that target B-cell receptor signalling, including ibrutinib, a Bruton's tyrosine kinase inhibitor,[12-15] and idelalisib, a phosphatidylinositol 3-kinase p110δ inhibitor,[16] and the humanised anti-CD20 monoclonal antibody obinutuzumab (GA101).[15,17-19] In pivotal trials, these agents were predominantly evaluated in patients with co-existing conditions or who were older; findings are only just emerging from trials in medically fit patients.[20-24]

Here, we describe a multicentre, phase II trial aimed to explore the efficacy of treatment induction with obinutuzumab and ibrutinib for nine months followed by an MRD-driven strategy for six additional months in previously untreated, medically fit patients with CLL and no 17p deletion. In the MRD-driven strategy, immunochemotherapy was given only in cases of partial response (PR) or detectable bone marrow MRD, and consisted of four cycles of FC and obinutuzumab, i.e. fewer than the standard six cycles of FCR, as based on results from the CLL2007 SA trial.[25] Primary objective was to determine whether this experimental strategy leads to a 30% or higher rate of CR with bone marrow MRD <0·01% at Month 16.

Methods

Study design and participants

ICLL-07 (NCT02666898) was a multicentre, open-label, phase II trial conducted by the French Innovative Leukemia Organization (appendix p 1).

Previously untreated, medically fit patients without any comorbidities (i.e. able to receive the combination FC and obinutuzumab, and with Cumulative Illness Rating Scale score ≤6) with Binet active stage A/B or stage C immunophenotypically confirmed B-cell CLL (iwCLL criteria) and no 17p deletion (<10% positive nuclei by fluorescence *in situ* hybridisation, FISH) were enrolled. Further inclusion criteria were: age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance status score <2; absolute neutrophil count ≥1 x 10^9/L (independent of growth factor support); platelets ≥100 x 10^9/L or ≥50 x 10^9/L if thrombocytopenia is related to the disease (each independent of transfusion support); adequate renal function (estimated glomerular filtration rate by Cockroft-Gault formula ≥60 mL/min/1·73 m^2); and adequate hepatic function (alanine and aspartate aminotransferase each ≤3x upper limit of normal [ULN], total bilirubin ≤1·5xULN, gamma glutamyltransferase ≤2·5xULN).

Main exclusion criteria were: previous CLL treatment except steroids for <1 month; life expectancy <6 months; known human immunodeficiency virus or B/C seropositivity; active haemolysis; active second malignancy currently requiring treatment (or <5 years CR after breast cancer); any severe comorbid conditions; concomitant disease requiring corticosteroids for >1 month; known hypersensitivity with anaphylactic reaction to humanised monoclonal antibodies or any study drug; contraindications for obinutuzumab or ibrutinib; transformation to aggressive B-cell malignancy; active infection; pregnancy/breastfeeding; and fertile men/women not using effective contraception.

The study was conducted in accordance with the Declaration of Helsinki, with ethical committee approval (Comité de Protection des Personnes, Lorraine, France) and written informed consent from all participants.

Procedures

During part 1 (treatment induction), all patients were planned to receive eight infusions of obinutuzumab 1000 mg iv over 6x4-weekly cycles (on Days 1/2 [100 mg D1 and 900 mg D2], 8 and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6), along with ibrutinib 420 mg po daily for nine months starting on Day 3 of Cycle 1. Doses on Days 1 to 4 of Cycle 1 were administered in hospital; other part 1 doses were administered as outpatients.

Part 2 (MRD-driven strategy) followed a first response assessment at Day 1 of Month 9, which included a whole-body computed tomography (CT) scan, bone marrow biopsy, and peripheral blood and bone marrow MRD testing. Patients underwent treatment depending on their clinical response and bone marrow MRD status. Patients in CR with bone marrow MRD <0·01% continued to receive only ibrutinib 420 mg po daily for six additional months. Patients in PR, or in CR with bone marrow MRD ≥0·01%, received 4x4-weekly cycles of FC (respectively 40 and 250 mg/m^2 po on Days 2 to 4 of each cycle) and obinutuzumab (1000 mg iv on Day 1 of each cycle), while continuing to receive ibrutinib 420 mg po daily for six additional months. For progressive disease (PD) or stable disease (SD), treatment discontinuation was planned.

With obinutuzumab, patients considered at high risk of an infusion-related reaction or tumour lysis syndrome (lymphocytosis >25 x 10^9/L) received prophylaxis and premedication for these risks. With all treatments, adverse events (AE) were managed according to the prescribing information, with dose modifications and/or medical treatment. Primary prophylaxis (herpes simplex virus, pneumocystosis) was mandatory.

Screening assessments (up to 28 days before treatment started) included demographic data and medical history, physical examination (including ECOG performance status and B symptoms), tumour lesion assessment (including peripheral nodes location and two-dimensional parameters) and vital signs, whole-body CT scan, full blood count, CD4/CD8 count, 12-lead electrocardiogram, and biochemistry assessments. Specific assessments included: FISH analysis for 17p13 deletion, 11q22 deletion, 13q14 deletion, and trisomy 12; and polymerase chain reaction analysis for immunoglobulin heavy gene variable (*IGHV*) status.

In part 1, before each obinutuzumab dose and at Day 1 of Month 9, and in part 2, before each cycle of FC and obinutuzumab or monthly during ibrutinib treatment alone, patients

underwent physical examination, full blood count, and biochemistry assessments (biological assessments were also performed on Day 22 of Cycle 1). Twelve-lead electrocardiogram was performed at Months 3 and 6.

Assessment of response to treatment induction was performed at Day 1 of Month 9 (i.e. three months after last cycle of obinutuzumab) and final evaluation of response was performed at Day 1 of Month 16 (i.e. three months after last cycle of FC and obinutuzumab). Response assessments included whole-body CT scan with tumour measurements, bone marrow trephine biopsy for patients in clinical CR, and MRD testing in both peripheral blood and bone marrow for all patients except those in PD or SD. Evaluation of clinical response was according to iwCLL 2008 criteria, by the investigators.[10] MRD testing was by eight-colour flow cytometry performed oligocentrally at four laboratories. The technique uses nine antibody markers (CD43, CD45, CD81, CD22 and CD79 in the same fluorescence channel, CD5, CD19, CD200, CD20), analysed in a single tube; limit of detection is 10^{-6} (with >10 million cells analysed per tube) and limit of sensitivity (obtained by testing serial dilutions of CLL cells) is 10^{-6}. In ICLL-07, the interpretation threshold of MRD <0·01% was applied, in accordance with iwCLL 2008 criteria (unchanged in 2018).[10,11] Only bone marrow MRD was decisional for the treatment strategy at Month 9; however MRD was tested in peripheral blood as well as in bone marrow, at the same time.

Beyond Month 16, clinical response was assessed every 3 months and MRD (in peripheral blood) only every 6 months, until Month 40.

AE were monitored throughout the study and reported according to National Cancer Institute Common Toxicity Criteria (version 4.03, June 2010); AE had to be reported within 8 days and serious AE (SAE) within 24 hours. The Data Safety and Monitoring Board examined all AE.

Outcomes

Primary endpoint was rate of CR with bone marrow MRD <0·01% at Day 1 of Month 16. Secondary endpoints included rate of CR with bone marrow MRD <0·01% at Day 1 of Month 9 and safety. Secondary survival endpoints reported are PFS and OS.

Statistical analysis

Primary endpoint was used to determine planned sample size. Following FCR in the CLL8 trial, CR rate was 44% and rate of bone marrow MRD <0·01% among the patients in CR was 44%.[1,5] Since bone marrow samples at final restaging were scheduled for MRD testing in patients considered to be in CR at initial response assessment (493/817 patients; 60%), rate of CR with bone marrow MRD <0·01% in the entire CLL8 trial cohort was 26%. Using a Fleming A'Hern one-stage design, a null hypothesis H0≤20% (based on minimum acceptable rate of efficacy at Day 1 of Month 16 of 20%) was tested against an alternative hypothesis H1≥30% (based on estimated rate of efficacy of 30%). With α risk of 5% and power 80%, if H0=0·2 and H1=0·3, 116 patients were required. Allowing for a 15% drop-out rate, planned sample size was 135 patients.

Final assessment of response at Day 1 of Month 16 was on intent-to-treat (ITT) basis, i.e. all patients included in the study. Response analyses for evaluable patients were performed at Day 1 of Month 9 and Day 1 of Month 16. Safety analyses included all patients who received at least one study treatment dose.

Statistical analysis software was R (version 3.4.4). Quantitative variables were described by the median and range; qualitative ones by counts and percentages. The primary endpoint was reported with a 90% confidence interval (CI), and compared to 20% with a one-sided exact binomial test at a significance level of 0·05. PFS and OS were plotted as Kaplan-Meier curves, with 2-year rates reported with 95% CI.

Role of the funding source

ROCHE and JANSSEN funded the study. The funders were involved in discussions about the ICLL-07 trial design and its objectives. The funders had no role in the collection, analysis and interpretation of the data, or in the writing of the report and decision to submit the paper for publication. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

Between 27 October 2015 and 16 May 2017, 135 patients (66% male; 34% female) were enrolled. Median age was 62 years, 62% of patients had ECOG performance status 0, 74% had Binet active stage A/B disease, and 56% had unmutated *IGHV* (Table 1). Analysis of *TP53* mutation status for the entire cohort, by next-generation sequencing, is ongoing.

In part 1, all patients were planned to receive obinutuzumab and ibrutinib (appendix p 1). At the first response assessment (Day 1 of Month 9), 130 patients were evaluable for response (Figure 1). Reasons for non-evaluability were two deaths (accidental fall at Month 7, unexplained sudden death at Month 8 [no autopsy, therefore relationship to treatment is unknown]) and three AE on Day 1 of Cycle 1 (acute coronary syndrome [no therapy given], listeria meningitis with disseminated intravascular coagulation [no therapy given], acute pulmonary oedema [hydration and obinutuzumab only given]). Ten of the 130 evaluable patients achieved CR with bone marrow MRD <0·01% at Day 1 of Month 9, a rate of 7·7% (appendix p 2). The remaining 120 evaluable patients were either in PR (75 patients; 58%) or achieved CR but with bone marrow MRD ≥0·01% (45 patients; 35%). In total, CR rate was 42% (55 patients) and PR rate was 58% (75 patients). Rate of bone marrow MRD <0·01% was 13% (17 patients). The *IGHV* mutational status (evaluable N=129; 1 patient in PR non-evaluable) did not appear to impact clinical responses; with *IGHV* mutated status (56 patients) and *IGHV* unmutated status (73 patients), all patients responded, and the CR rate was 46% and 40%, respectively.

In part 2, based on the MRD-driven strategy (appendix p 1), ten patients (7.7%, with CR and bone marrow MRD <0·01%) were planned to receive ibrutinib alone for six additional months and 120 patients (92%) were planned to receive 4x4-weekly cycles of FC and obinutuzumab, along with ibrutinib for six additional months (Figure 1). At the primary response assessment (Day 1 of Month 16), in the ITT population, 62% of patients (84/135, 90% CI: 55%−69%) achieved CR with bone marrow MRD <0·01% (Table 2). This percentage is statistically different from 20% (p<0·0001). All patients meeting this primary endpoint also had peripheral blood MRD <0·01%. The ITT CR rate was 73% (99 patients), the ITT bone marrow MRD <0·01% rate was 79% (107 patients), and the ITT peripheral blood MRD <0·01% rate was 85% (115 patients) (Figure 2). A total of 123 patients were

evaluable for response (Figure 1). Reasons for non-evaluability were five AE (haemorrhagic renal cyst, renal carcinoma, brain haemorrhage, thrombocytopenia, permanent atrial fibrillation), one SD, and one patient consent withdrawal. Ten further patients were not evaluable for bone marrow MRD, due to missing results, meaning that 113 patients were evaluable for both response and bone marrow MRD. Of these patients, 74% (84/113, 90% CI: 67%−81%) achieved CR with bone marrow MRD <0·01% (Table 2); the CR rate was 80% (99/123) and the bone marrow MRD <0·01% rate was 95% (107/113) (Figure 2). All ten patients treated with ibrutinib alone in part 2 remained in CR at Month 16; eight were evaluable for bone marrow MRD and all remained with <0·01% at Month 16.

In part 1, 92% (124/135) of patients received the planned eight infusions of obinutuzumab. Ibrutinib dosage was reduced in four patients and ibrutinib was permanently discontinued in three patients due to an AE (atrial fibrillation, atrial flutter, neutropenia). Of the 133 patients who received at least one study treatment dose and were included in the safety population, Grade 3 or higher toxicity was reported in 58% (77/133) of patients. Neither death was considered study drug-related. Grade 3/4 haematological toxicities included thrombocytopenia (32% of patients; 42/133), neutropenia (24%; 32/133), and anaemia (5%; 7/133) (Table 3). Infusion-related reactions mostly occurred on Day 1 of Cycle 1 and were reported in 71% (94/133) of patients at any grade and in 8% (11/133) of patients at Grade 3/4.

In part 2, among the 120 patients planned to receive FC and obinutuzumab, alongside ibrutinib, 96% (115 patients) received at least one cycle and 88% (105 patients) received all four cycles (Figure 1). Ibrutinib was permanently discontinued in 16% of patients (19/120) in the ibrutinib plus FC and obinutuzumab arm and none (0/10) in the ibrutinib alone arm. Ibrutinib dosage was reduced in a total of 20% of patients in part 2 (26/130) due to Grade 4 haematological toxicity. No further death occurred in part 2. Grade 3/4 toxicity was reported in 38% (49/130) of patients. Grade 3/4 haematological toxicities included neutropenia (24% of patients; 31/130), thrombocytopenia (15%; 19/130), and anaemia (5%; 6/130); 3% of patients (4/130) experienced Grade 3/4 febrile neutropenia (Table 3). Grade 3/4 non-haematological toxicities included gastrointestinal disorders (10% of patients; 13/130) and cardiac events (2·3%; 3/130).

Over the entire experimental strategy, three deaths were reported, including one accidental fall at Month 7 and one unexplained sudden death at Month 8 in part 1. No death occurred in part 2. One death due to Hodgkin lymphoma Epstein-Barr virus-associated

haemophagocytosis syndrome occurred at Month 23, i.e. seven months after the last FC and obinutuzumab cycle.

A total of 49 SAE were observed (27 part 1; 22 part 2) (appendix p 3). Most frequent categories of SAE were infections (10 events), cardiac events (8), and haematological events (8).

With a median follow-up of 26.3 months (interquartile range 25.3–27.1 months), the 2-year PFS rate was 98% (95% CI: 95%–100%) (Figure 3A) and the 2-year OS rate was 99% (95% CI: 96%–100%) (Figure 3B).

Discussion

This ICLL-07 trial demonstrated that treatment induction with obinutuzumab and ibrutinib for nine months followed by an MRD-driven strategy achieved a 62% ITT rate of CR with bone marrow MRD <0·01% at Month 16 in previously untreated, medically fit patients with CLL and no 17p deletion. The 62% efficacy rate was high, especially since calculated by ITT (85 of all 135 patients enrolled), and more than double that typically reported for six cycles of FCR (under 30%); the primary objective was thus exceeded by far.[3-6,8] The rate is superior to that reported for any first-line regimen based on chemotherapy plus rituximab.[3-7,8,25] A feature of our experimental strategy is that patients received study treatment for a definite period of time (total 15 months).

Our approach of treatment induction with obinutuzumab and ibrutinib, followed by an MRD-driven strategy in which immunochemotherapy was given only in cases of PR or detectable bone marrow MRD, was a concept designed to minimise chemotherapy-related toxicity whilst optimising efficacy. There is increasing interest in potentially sparing medically fit patients with CLL from chemotherapy by using strategies incorporating non-chemotherapeutic agents, in particular ibrutinib, obinutuzumab, and venetoclax.[20-23,26,27] In the previous ILLUMINATE trial, a combination of obinutuzumab (six cycles) and ibrutinib (until disease progression), without chemotherapy, in patients with co-existing conditions or who were older, yielded a CR rate of 19% and bone marrow MRD <0·01% rate of 20%.[15] In the CLL2-BIG trial, 30 previously untreated patients enrolled irrespective of comorbidities received treatment induction with six cycles of obinutuzumab and ibrutinib (with or without prior bendamustine debulking), followed by an MRD-triggered maintenance phase.[28] At the end of treatment induction, 40% of patients were in CR and 53% had peripheral blood MRD <0.01%; bone marrow MRD results were not reported and the maintenance phase was ongoing. Although trial comparisons can be made only with caution, in ICLL-07, following the obinutuzumab and ibrutinib treatment induction, only 7·7% reached CR with bone marrow MRD <0·01%, and thus in accordance with the MRD-driven strategy continued to receive only ibrutinib for six additional months. Most patients went on to receive four cycles of FC and obinutuzumab, alongside ibrutinib for six additional months. The 62% ITT rate of CR with peripheral blood and bone marrow MRD <0·01% was achieved

with no more than four cycles of FC; the constituent CR rate was 73% and peripheral blood and bone marrow MRD <0·01% rate was 79%.

To our knowledge, all other trials evaluating first-line strategies incorporating obinutuzumab and/or ibrutinib in medically fit patients with CLL have included upfront chemotherapy.[20,22-24] The phase 1b GALTON trial enrolled only previously untreated, medically fit patients and yielded a CR or incomplete CR (CR/CRi) rate of 24% among 21 patients treated with obinutuzumab plus FC and 45% among 20 patients treated with obinutuzumab plus bendamustine; MRD rate was not reported.[23] The phase 3b GREEN trial used investigator's choice of obinutuzumab-based treatment in 631 previously untreated patients (339 fit, 292 unfit).[22] The CR/CRi rate was 36% for obinutuzumab plus bendamustine and 46% for obinutuzumab plus FC;[22] the bone marrow MRD <0·01% rate was 68% and not reported, respectively.[29] In a phase II trial, presented at the 2017 American Society of Hematology (ASH) meeting, 35 young, medically fit, previously untreated patients received ibrutinib plus six FCR cycles followed by ibrutinib maintenance therapy.[24] The rate of CR with bone marrow MRD <0.01% was 37% post FCR and 57% post ibrutinib maintenance therapy. Of note, a phase II trial conducted at the US MD Anderson Cancer Center and presented at ASH 2018 provided further support for an obinutuzumab and ibrutinib-based MRD-driven approach in previously untreated, medically fit patients.[20] The trial enrolled patients with *IGHV* mutated status and no 17p deletion and all patients initially received three cycles of ibrutinib, FC and obinutuzumab; then, patients in CR/CRi with bone marrow MRD <0·01% went on to receive ibrutinib plus obinutuzumab for three further cycles followed by ibrutinib alone for six cycles, whilst those in PR or with detectable bone marrow MRD went on to receive ibrutinib plus obinutuzumab for nine further cycles. Among 43 patients enrolled, the rate of CR with bone marrow MRD <0·01% after three cycles was 40%. At the time of reporting, a total of 28 patients had reached the 12-month timepoint and all had bone marrow MRD <0·01%. By contrast with our experimental strategy where all patients received obinutuzumab and ibrutinib (chemotherapy-free) treatment induction, in the US trial all patients received three cycles of upfront FC in addition to obinutuzumab and ibrutinib.[20] The US trial also differed in that *IGHV* mutated status was an inclusion criterion. In ICLL-07, patients were enrolled irrespective of *IGHV* mutational status, and the CR rate following obinutuzumab and ibrutinib treatment induction was similar irrespective of *IGHV* mutated and unmutated status (46% and 40%, respectively).

Interim results were also presented at ASH 2018 from a phase II trial in which 80 previously untreated patients with CLL and at least one high-risk feature (17p deletion, *TP53* mutation, 11q deletion, *IGHV* unmutated, age ≥65 years) initiated ibrutinib for three cycles followed by ibrutinib plus venetoclax for 24 cycles.[26] Among 25 patients who had reached 12 months of the combination, 92% were in CR/CRi and 68% had bone marrow MRD <0·01%. Ongoing phase III trials are also evaluating ibrutinib (given until disease progression) plus six cycles of rituximab, compared to six FCR cycles, in previously untreated, medically fit patients.[21,27] Interim findings, again presented at ASH 2018, suggested that the ibrutinib and rituximab combination was favourable compared to FCR in terms of PFS and OS.[21]

The high efficacy rate determined with our experimental strategy is ratified by the quality of the response assessments. Our data collection was exhaustive, with 84% (113/135) of patients evaluable for both clinical response and bone marrow MRD at Month 16. The international iwCLL 2008 criteria[10] (relevant criteria unchanged in 2018)[11] were followed for response and MRD evaluation. For response assessment, all patients had a whole-body CT scan and those in clinical CR had a bone marrow biopsy. For assessment of MRD, flow cytometry techniques classically have demonstrated sensitivity of 10^{-4}.[30,31] The eight-colour flow cytometry technique used in ICLL-07, and other FILO group trials,[8] has demonstrated considerably greater sensitivity of 10^{-6}, but for consistency with the iwCLL criteria, we applied the 10^{-4} (0·01%) interpretation threshold.

Concerning the safety profile of the experimental strategy, the most common treatment-emergent Grade 3/4 AE rates during parts 1 and 2 were 32% and 15% thrombocytopenia, 24% and 24% neutropenia, 5% and 5% anaemia, 1·5% and 3% febrile neutropenia, 3% and 10% gastrointestinal disorders, and 2·3% and 2·3% cardiac events, respectively. No new or unexpected AE occurred compared to those previously reported with a combination of immunochemotherapy. This toxicity remains important, and comparable to the reported Grade 3/4 AE rates with first-line standard FCR treatment (total 76%)[1] or with first-line ibrutinib, FC and obinutuzumab for patients with *IGHV*-mutated CLL (40% thrombocytopenia, 46% neutropenia, 10% febrile neutropenia, 7% atrial fibrillation).[20]

A study limitation is that ICLL-07 is single-arm trial with no control arm. We do not yet know to what extent the CR with MRD <0.01% responses will persist beyond the end of the definite treatment period of 15 months, but a planned assessment of the MRD evolution over time is ongoing. Survival data are not mature, but the trial remains ongoing for planned

assessments of survival endpoints. Since bone marrow MRD <0·01% has demonstrated evidence as a surrogate marker for PFS[4,5,7,9] we hypothesise that the high rate of CR with peripheral blood and bone marrow MRD <0·01% will translate into prolonged PFS following the study treatment discontinuation per protocol. However, in the absence of a randomised trial, we will be unable to conclude on whether obtaining CR with MRD <0·01% with our experimental strategy translates into improved outcomes (even when the survival data become available).

In conclusion, the ICLL-07 trial determined that treatment induction with obinutuzumab and ibrutinib followed by an MRD-driven strategy yielded a 62% ITT rate of CR with bone marrow MRD <0·01%. ICLL-07 was, to our knowledge, the first trial to explore treatment induction with obinutuzumab and ibrutinib followed by an MRD-driven strategy in which immunochemotherapy was given only in cases of PR or detectable bone marrow MRD. The efficacy rate of 62% ITT is superior to that reported for any first-line regimen based on chemotherapy plus either rituximab or only obinutuzumab. Longer-term survival and MRD outcomes from ICLL-07, and other trials evaluating first-line strategies incorporating non-chemotherapeutic agents in medically fit patients with CLL, are eagerly awaited.

Contributors

VR was head of project, responsible for regulatory authorisation and following data collection. PF and ASM performed a literature search. PF, ASM, LY, VL, OT, RL, ViL, FC, and AD contributed to the study design. VR, PF, and ASM collected data. FS, ASM, and PF analysed and interpreted the data.

ASM and PF drafted the report, with medical writing assistance from Cath Carsberg, PhD, and all authors (MSD, FS, VR, BM, KL, BV, GS, OT, AD, CP, BP, VL, CT, SDG, FO, AB, PC, GC, LMF, LY, CD, MTG, JPV, TA, FC, SL, ViL, FNK, MLGT, CA, MT, RL) revised the report for important intellectual content and approved the final version.

Declaration of Interests

[Need to add details for MSD, BM, BV, CP, CT, SDG, FO, LY, MTG, TA, FNK]

KL reports grants from Takeda, personal fees from Amgen, Gilead, and Janssen, and grants and personal fees from Abbvie, Novartis, Roche, and Sandoz.

GS reports grants and personal fees from Roche, and personal fees from Abbvie, Acerta, Amgen, Bristol-Myers Squibb, Celgene, Epizyme, Gilead, Janssen, Merck, Morphosys, Novartis, Pfizer, and Servier.

OT reports personal fees from Takeda, and personal fees and non-financial support from Abbvie, Gilead, Janssen, Roche, and Sandoz.

AD reports personal fees and non-financial support from Abbvie, Gilead, Janssen, and Roche.

VL reports personal fees and non –financial support from Abbvie, Gilead, Janssen and Roche

BP reports personal fees from Celgene, Janssen, Sebia, and Takeda.

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CD reports personal fees from Janssen, non-financial support from Gilead, and personal fees and non-financial support from Abbvie and Roche.

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MLGT reports personal fees from Alexion Pharma France.

RL reports personal fees from Abbvie, non-financial support from Janssen, and personal fees and non-financial support from Alexion.

PF reports personal fees and non-financial support from Abbvie, Gilead, Janssen, and Roche.

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ASM, FS, VR, AB, SL, CA, JPV and MT declare no competing interests.

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Data sharing

Individual participant data are not available. The study protocol is available from: https://clinicaltrials.gov/ct2/show/NCT02666898. For original data please contact: p.feugier@chru-nancy.fr. A protocol synopsis is included in the appendix (p 7).

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Tables and figures

Table 1: **Patients and disease characteristics at baseline**

	Patients (N=135)*
Age, median years (range)	62 (35–80)
Male / female, n (%)	89 (66%) / 46 (34%)
ECOG 0 / 1 / 2, n (%)	84 (62%) / 50 (37%) / 1 (1%)
Lymphocytes, median 10^9/L (range)	75·4 (2·3–433)
Haemoglobin, median 10^9/L (range)	12·65 (6·5–16·5)
Platelets, median 10^9/L (range)	152 (49–444)
Binet stage, n (%)	
A with active disease	9 (7%)
B with active disease	91 (67%)
C	35 (26%)
***IGHV* mutational status, n/N (%)**	
Mutated	59/133 (44%)
Unmutated	74/133 (56%)
Cytogenetics, n/N (%)	
11q deletion	30/117 (26%)
13q deletion	60/117 (51%)
Trisomy 12	25/117 (21%)
Complex karyotype (5 abnormalities)	18/117 (15%)
β-microglobulin, median mg/L (range)	3·6 (1·5–7·5)
Creatinine clearance (Cockroft), median mL/min (range)	82 (42–173·5)

*N=135, unless otherwise stated

IGHV, immunoglobulin heavy gene variable

Table 2: **Clinical and MRD (peripheral blood and bone marrow) responses at Day 1 of Month 16 (evaluable patients)**

MRD in PB / BM	CR	PR	All
Ibrutinib in part 2 (N=10)	**10**	**0**	**10**
PB <0·01% / BM <0·01%	8*	0	8
PB <0·01% / BM not evaluable	2	0	2
Ibrutinib + FC + obinutuzumab in part 2 (N=113)	**89**	**24**	**113**
PB <0·01% / BM <0·01%	76*	23	99
PB ≥0·01% / BM ≥0·01%	5	1	6
PB <0·01% / BM not evaluable	6	0	6
PB and BM not evaluable	2	0	2
All in part 2	**99**	**24**	**123**

*Eighty-four patients had CR with BM MRD <0·01%

BM, bone marrow; CR, complete response; MRD, minimal residual disease;
PB, peripheral blood; PR, partial response

Table 3: **Most common Grade 1/2 adverse events (≥10% of patients) and all Grade 3/4 adverse events in part 1 and part 2, by patients (safety population)**

	Part 1 (N=133) Grade 1/2 n (%) of patients	Part 1 (N=133) Grade 3 n (%) of patients	Part 1 (N=133) Grade 4 n (%) of patients	Part 2 (N=130) Grade 1/2 n (%) of patients	Part 2 (N=130) Grade 3 n (%) of patients	Part 2 (N=130) Grade 4 n (%) of patients
Haematological AE						
Thrombocytopenia	45 (34%)	22 (17%)	20 (15%)	43 (33%)	10 (8%)	9 (7%)
Neutropenia	14 (11%)	17 (13%)	15 (11%)	15 (12%)	20 (15%)	11 (8%)
Anaemia	26 (20%)	5 (4%)	2 (1.5%)	34 (26%)	3 (2·3%)	3 (2·3%)
Febrile neutropenia	-	2 (1·5%)	-	-	2 (1·5%)	2 (1·5%)
Non-haematological AE						
Gastrointestinal disorders	14 (11%)	4 (3%)	-	62 (48%)	10 (8%)	3 (2·3%)
Cardiac events	-	-	3 (2·3%)	-	-	3 (2·3%)
Infusion-related reactions	83 (62%)	7 (5%)	4 (3%)	-	-	-

Tissue disorders	13 (10%)	-	-	-	-	-
Hepatobiliary disorders	13 (10%)	-	-	-	-	-

AE, adverse event

Three grade 5 events included: one sudden death at Month 8; one accidental fall at Month 7; one death due to Hodgkin lymphoma Epstein Barr virus-associated haemophagocytosis syndrome at Month 23

Figure legends

Figure 1: **Patient disposition**

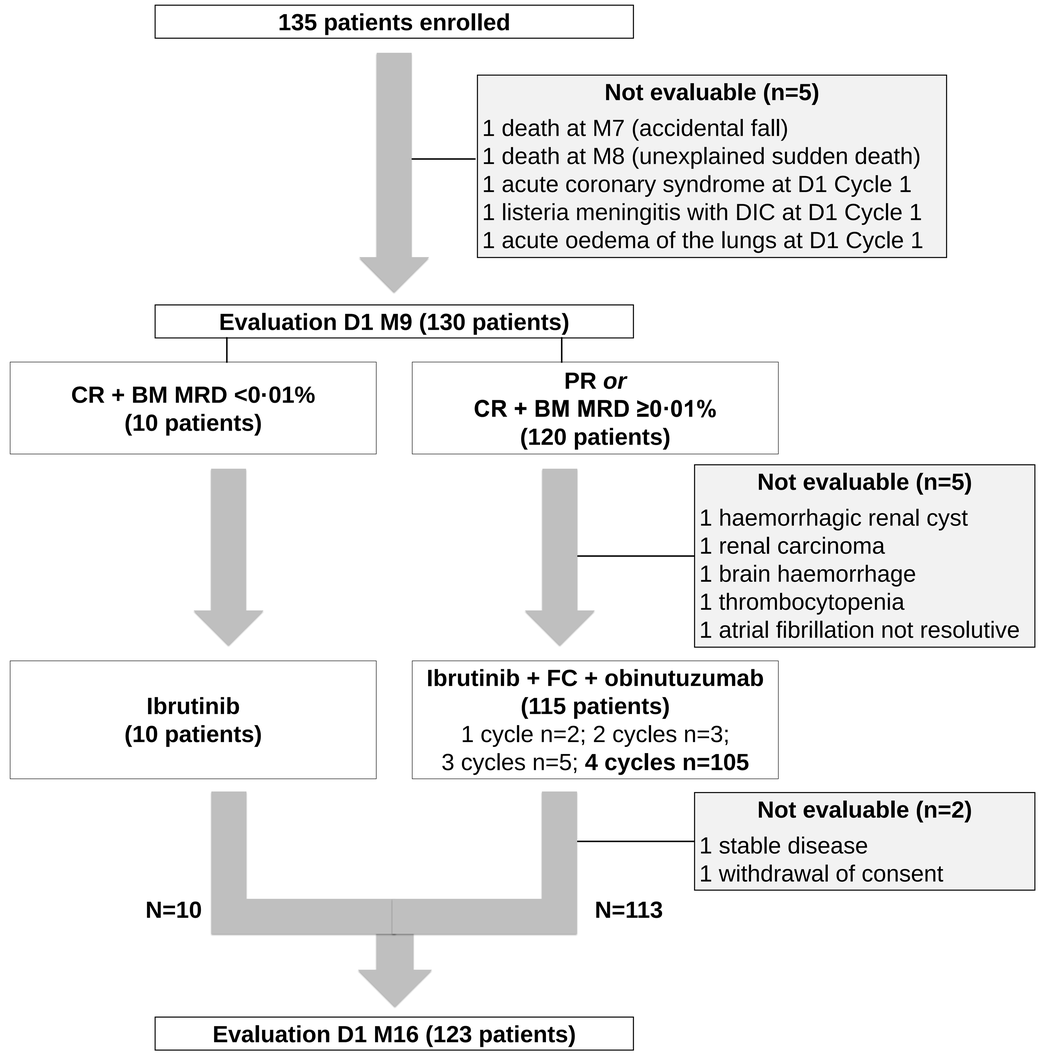
BM, bone marrow; CR, complete response; D, day; DIC, disseminated intravascular coagulation; FC, fludarabine + cyclophosphamide; ITT, intent-to-treat; M, month; MRD, minimal residual disease; NE, not evaluable; PR, partial response

Figure 2: **Clinical and MRD responses at Day 1 of Month 16 (ITT and evaluable populations).** A) Clinical (iwCLL) response. B) MRD in peripheral blood and bone marrow

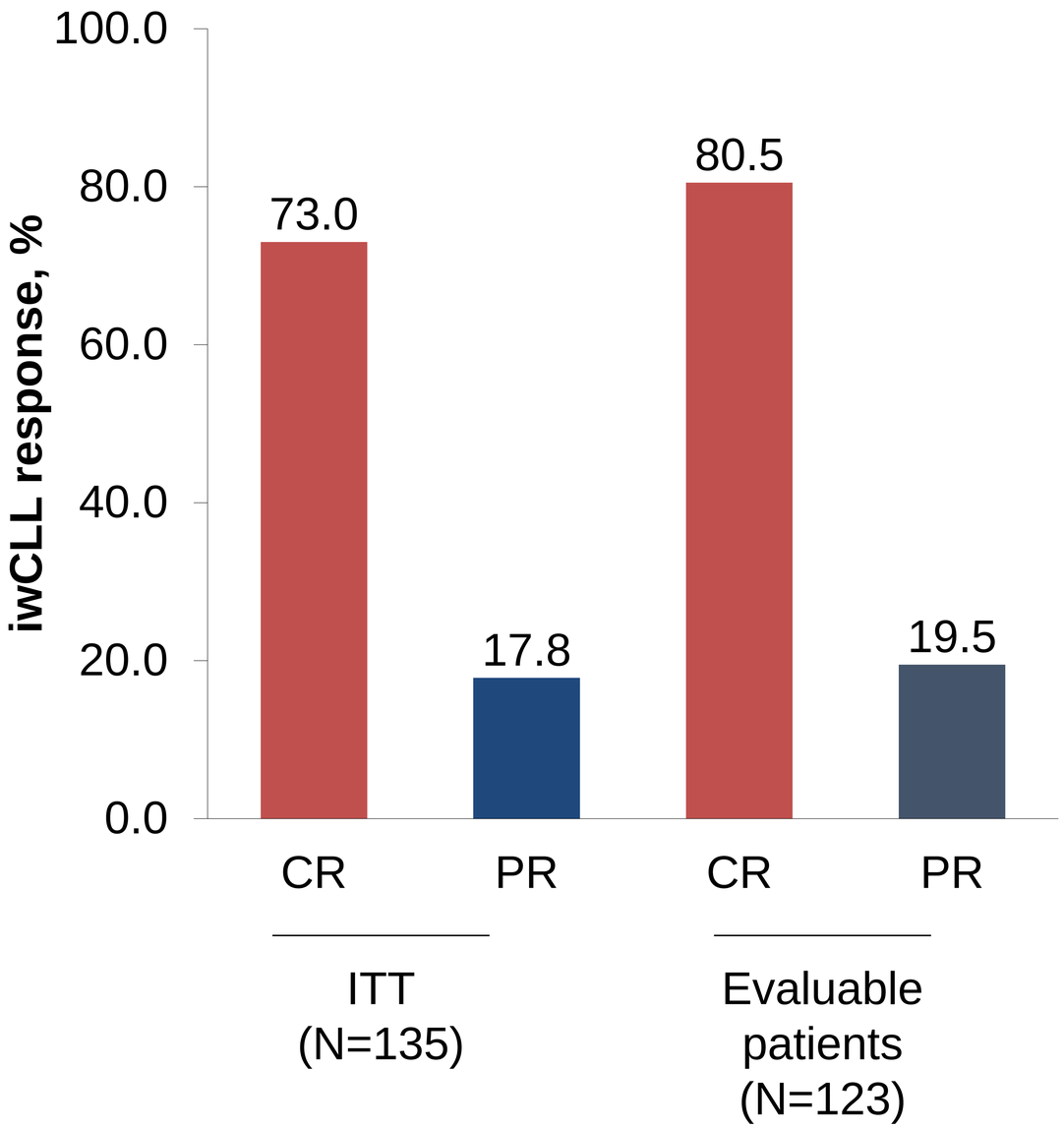
BM, bone marrow; CR, complete response; ITT, intent-to-treat;
iwCLL, International Workshop on Chronic Lymphocytic Leukemia;
MRD, minimal residual disease; PB, peripheral blood; PR, partial response

MRD was not evaluable in 22 patients: 12 without iwCLL response evaluation; 8 with PB MRD <0·01% but without BM MRD assessment; 2 without PB or BM MRD assessment

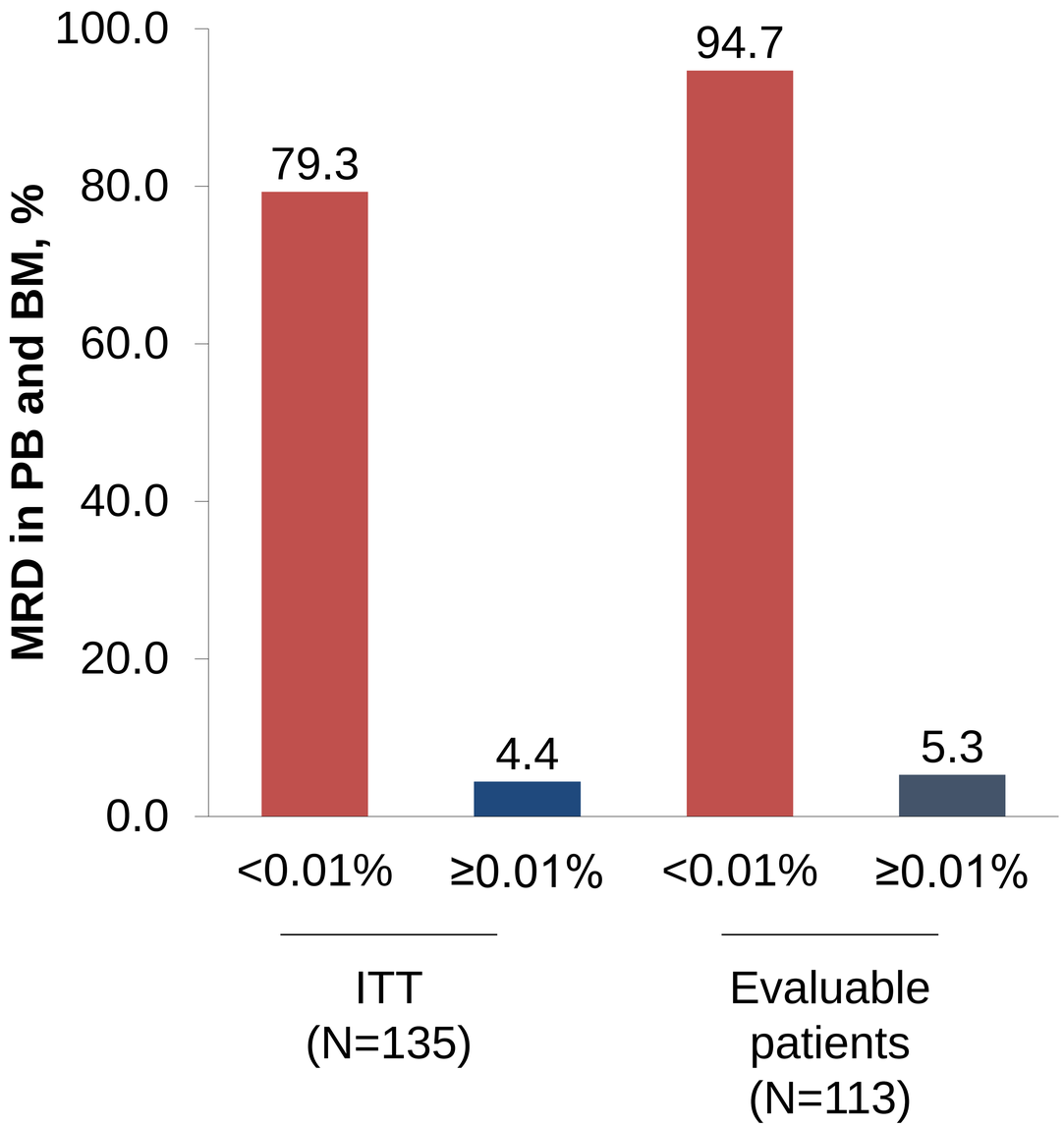
Figure 3: **Kaplan-Meier survival curves (evaluable populations).** A) Progression-free survival (N=133, 4 events). B) Overall survival (N=133, 3 events). Two patients were excluded from survival analyses because they did not begin any therapy (due to acute coronary syndrome or listeria meningitis with disseminated intravascular coagulation on Day 1 of Cycle 1)

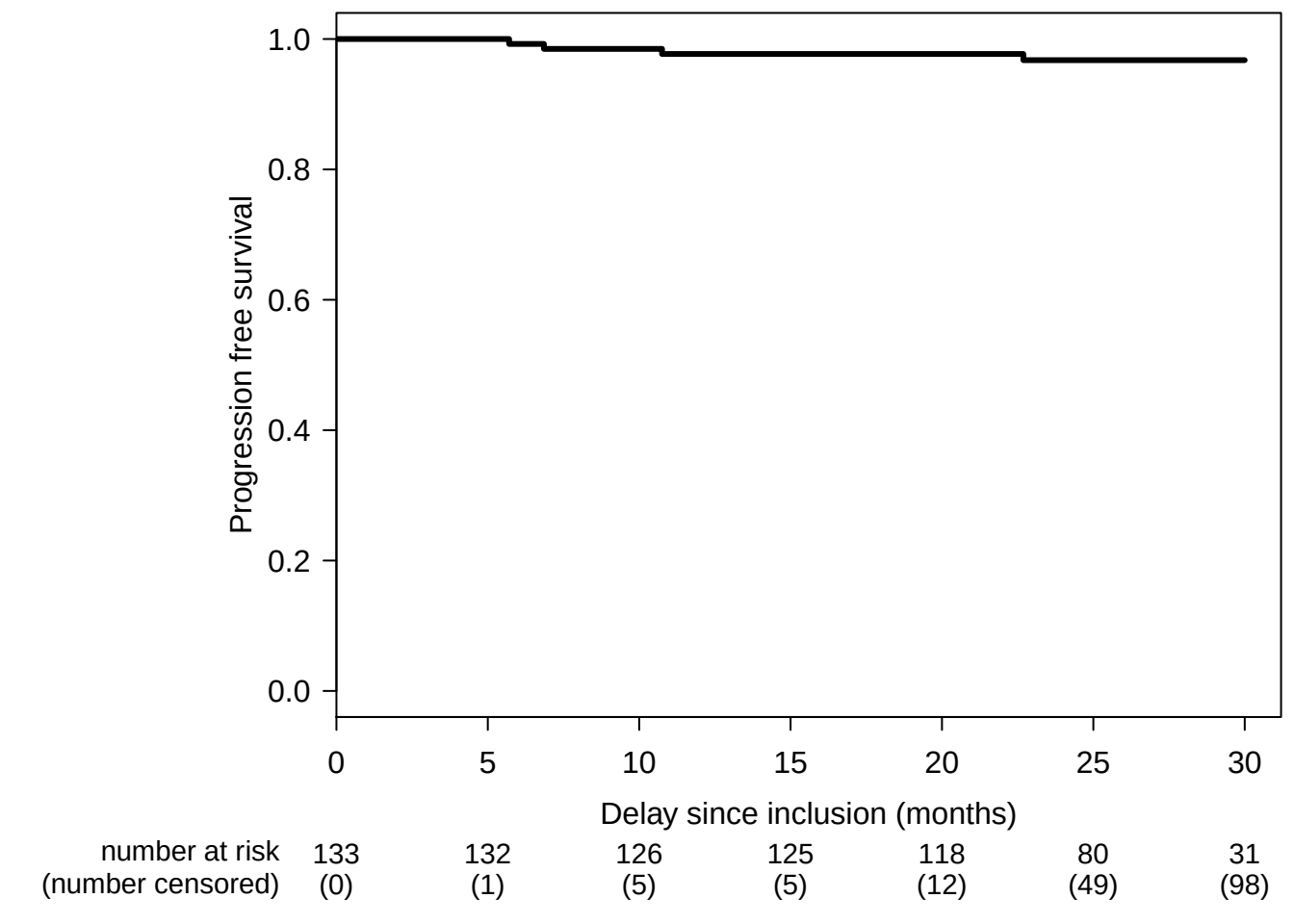

135 patients enrolled
Not evaluable (n=5)
1 death at M7 (accidental fall)
1 death at M8 (unexplained sudden death)
1 acute coronary syndrome at D1 Cycle 1
1 listeria meningitis with DIC at D1 Cycle 1
1 acute oedema of the lungs at D1 Cycle 1
Evaluation D1 M9 (130 patients)
CR + BM MRD <0·01%
(10 patients)
PR or
CR + BM MRD ≥0·01%
(120 patients)
Not evaluable (n=5)
1 haemorrhagic renal cyst
1 renal carcinoma
1 brain haemorrhage
1 thrombocytopenia
1 atrial fibrillation not resolutive
Ibrutinib
(10 patients)
Ibrutinib + FC + obinutuzumab
(115 patients)
1 cycle n=2; 2 cycles n=3;
3 cycles n=5; 4 cycles n=105
Not evaluable (n=2)
1 stable disease
1 withdrawal of consent
N=10
N=113
Evaluation D1 M16 (123 patients)

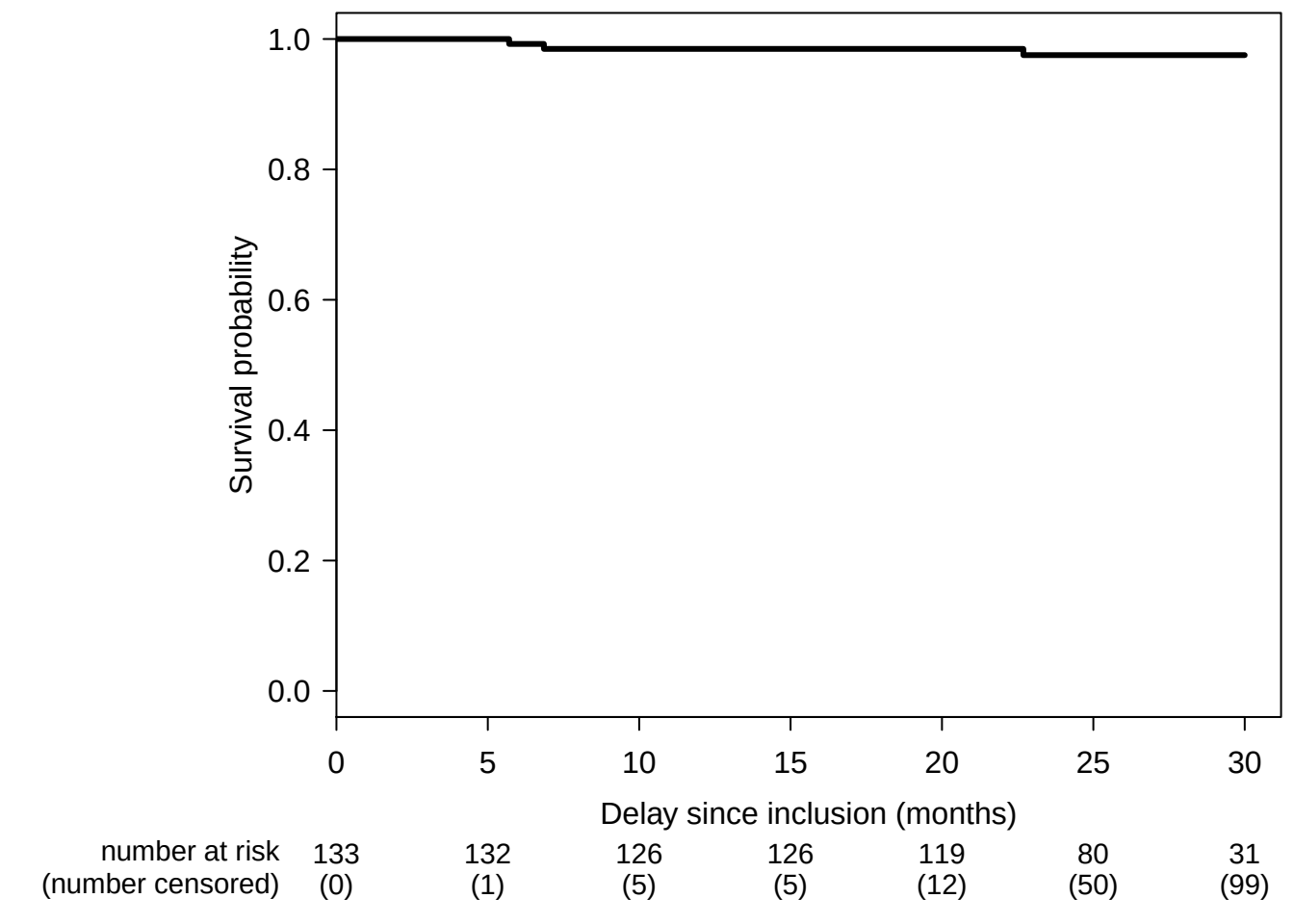
A


100.0
80.0
60.0
40.0
20.0
0.0
iwCLL response, %
73.0
17.8
80.5
19.5
CR
PR
CR
PR
ITT (N=135)
Evaluable patients (N=123)

B


100.0
80.0
60.0
40.0
20.0
0.0
MRD in PB and BM, %
79.3
4.4
94.7
5.3
<0.01%
≥0.01%
<0.01%
≥0.01%
ITT (N=135)
Evaluable patients (N=113)


1.0
0.8
0.6
0.4
0.2
0.0
Progression free survival
0
5
10
15
20
25
30
Delay since inclusion (months)
number at risk 133 132 126 125 118 80 31
(number censored) (0) (1) (5) (5) (12) (49) (98)


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
0
5
10
15
20
25
30
Delay since inclusion (months)
number at risk
(number censored)
133
(0)
132
(1)
126
(5)
126
(5)
119
(12)
80
(50)
31
(99)